REMARKS/ARGUMENTS

Claims 14-16, 18-25 and 27-36 are pending in the application. Claims 1-13, 17 and 26 have been canceled. Claims 14-25 and 27-36 are rejected. Applicant has amended claim 14 and submits the following remarks in support of the patentability of the pending claims, as amended.

Applicant first wishes to emphasize that the outstanding office action is the fifth office action in this case, in which Applicant has been required to file two RCEs in order for arguments to be fairly considered. In this series of office actions, the examiner has repeatedly relied on certain prior art references, which applicant has distinguished over, the examiner has then withdrawn, and the examiner has then resurrected again in subsequent office actions, repeating the same mischaracterizations of the prior art that Applicant has previously distinguished over. In the present office action, the examiner again relies on this same prior art (i.e., Ruano et al. and Rao et al.), notwithstanding these references clearly fail to disclose or suggest numerous elements of the claimed invention. This pattern of repeated rejections, based on art that has previously been distinguished over, withdrawn and then resurrected, constitutes "piecemeal examination" which not only wastes precious time and financial resources of the Applicant and the USPTO, but also results in significant prejudice to Applicant through loss of patent term (this application was filed on March 7, 2001, and has been pending now for over 5 years!). The examiner has had ample opportunity to identify relevant prior art and present arguments as to the patentability of the claimed invention, but, as explained in detail below, the prior art relied upon by the examiner still fails to teach or suggest key claim limitations. Applicant respectfully requests that this "piecemeal examination" and repeated reliance on obviously irrelevant prior art be discontinued. Applicant has amended the claims herein to recite certain elements directly as structures, in order to address the examiner's concerns regarding "intended use limitations." These claim amendments have been made so as to place the claims in condition for appeal, which Applicant will file in the event these unfounded rejections are maintained. Applicant urges the examiner to fairly consider the *differences* between the *claimed* invention and the cited references, and allow those claims that recite subject matter not taught or suggested in the cited reference.

Summary of Invention

The present invention is generally directed to a kit consisting of a single reaction vessel for each region of the DNA to be sequenced, where each reaction vessel contains sequencing primers specific for the sense strand and sequencing primers specific for the anti-sense strand of the region of DNA to be sequenced. The sequencing primers specific for the sense strand and sequencing primers specific for the anti-sense strand are also labeled with a distinguishable detectable label.

The kits of the present invention are made possible as a result of methods and systems that have been previously been determined by the United States Patent and Trademark Office to be patentable (see, e.g., U.S. Patent Nos. 5,789,168; 5,830,657; 5,888,736; 6,083,699; and 6,214,555, to which patents the present application claims priority). The above-referenced patents describe and claim methods and systems for simultaneous PCR amplification and direct sequencing of multiple target DNAs, a methodology now commonly referred to as "CLIP sequencing." CLIP sequencing is essentially a patentable improvement on the coupled amplification and sequencing method of Ruano et al., in that CLIP sequencing (1) utilizes an improved engineered mutant of thermostable DNA polymerase that lacks 5′-3′ exonuclease activity that is capable of incorporating chain terminating dideoxynucleotides into an extending nucleic acid polymer at higher rates relative to the rate of incorporation of deoxynucleotides, thereby producing uniform band intensities, and (2) utilizes two inward-facing primers having distinguishable detectable labels to generate sequencing fragments for the sense and anti-sense DNA strands. Consequently, CLIP sequencing can be used to simultaneously amplify and sequencing substantially natural abundance DNA, and represents a novel methodology that enables and provides utility to kits that combine multiple primers, one specific for the sense strand of DNA and the other for the anti-sense strand of DNA, in a single reaction vessel, for obtaining bi-directional sequence of a target region of DNA. The kits of the present invention are therefore useful for diagnostic sequencing of DNA samples, and reduce risk of error and contamination, increase the ease with which the procedure can be automated, and thereby potentially decrease the marginal costs in terms of equipment and labor for performing the test, as well as increase the reliability and accuracy of such tests.

Objection to Improper Dependency

Claim 17 is objected to because it depends from a cancelled claim 13. Claim 17 has accordingly been canceled, thereby obviating the rejection. Withdrawal of the objection is therefore requested.

Rejection Under 35 USC 102(e)

Claims 14-17, 20-22, 25, 27-29, and 32-34 are rejected under 35 U.S.C. §102(e) as being anticipated by Digby et al. (U.S. 6,432,634) (referred to herein as "Digby"). Applicant traverses this rejection on the basis that Digby does not disclose each and every element of the claimed invention.

The claimed invention recites kits for sequencing one or more DNA regions from a genomic DNA sample or microorganism. The claimed kit consists of (1) "a single reaction vessel for each DNA region to be sequenced," and (2) each reaction vessel contains "a mixture of region-specific sequencing reagents sufficient for sequencing the sense and anti-sense strand of each DNA region to be sequenced." The claims further recite that the region-specific sequencing reagents "comprise region-specific sequencing primers comprising (a) "a primer which specifically binds to the sense strand of said DNA region" and is "labeled with a first detectable label" and (b) "a primer which specifically binds to the antisense strand of said DNA region" and is "labeled with a second detectable label that is distinguishable from the first detectable label." The two primers also must "flank one of the DNA regions." Optionally, the kit may contain (3) "one or more non-region specific sequencing reagents."

Digby, on the other hand, does not disclose each and every element of the claimed invention, as described above. Specifically, Digby discloses a sequencing kit that includes multiple containers, with each container having one or more sequencing primer for generating a single type of nucleotide base (A, G, C or T). Thus, one container includes sequencing primers for generating chain termination fragments ending with an "A" base. A second container includes sequencing primers for generating chain termination fragments ending with a "G" base, and so forth. Because separate containers are required for each of the four different nucleotide base types, four containers are required to obtain the complete sequence of each gene.

Furthermore, although each container may include multiple primers for different genes, each gene region still requires four reaction vessels.

The Digby reference thus does not disclose the following claimed elements:

- "a *single* reaction vessel for *each DNA region* to be sequenced";
- a reaction vessel which contains "a mixture of region-specific sequencing reagents sufficient for sequencing the *sense and anti-sense strand* of each DNA region to be sequenced";
- "a primer which specifically binds to the *sense* strand of said DNA region" and is "labeled with a first detectable label" *and* "a primer which specifically binds to the *antisense* strand of said DNA region"; and
- the two primers "flank one of the DNA regions."

In view of the fact that Digby fails to teach the above claim limitations, Digby does not anticipate the claimed invention.

In the outstanding office action, it should further be noted that the examiner mischaracterizes the teachings of Digby, and then compounds the error by relying on the mischaracterization in support of the claim rejection. Specifically, the examiner states that "Digby et al. teach a kit for sequencing a specific region from a gene, said kit consisting of, in package [sic] combination *at least one reaction vessel* or a plurality of reaction vessels for each of the regions to be sequenced containing a mixture of a plurality of sequencing primers, one for each gene region to be evaluated." (Office Action, page 3, lines 1-3). Digby does not, however, teach that any single region of a nucleotide can be sequenced with "one reaction vessel." To the contrary, Digby teach that each region requires four reaction vessels, each of which contains primers and reagents for one of the four different chain termination fragment base types! For example, Digby specifically states that "In this method, each sample is first divided into four aliquots which are combined with four sequencing reaction mixtures" (column 1, lines 54-56). Figure 1B of Digby also clearly shows four reaction vessels labeled "A REACTION", "B REACTION", "C REACTION," and "D REACTION." Thus, Digby teach that four reaction vessels are required, not one. The examiner's statement that Digby teaches "one reaction vessel" for each region to be sequenced is simply incorrect.

Furthermore, the examiner argues that the "binding of the primers to the sense and antisense strands of the DNA in a desired sample is an inherent property of the primers." This statement is unclear, if not incorrect and misleading. At the very least, the statement is unclear in that it does not identify which "primers" have the "inherent property" of binding to both the sense and the anti-sense strand. The examiner makes no reference to what primers in Digby are being referred to, and Applicant is therefore unable to respond to such a vague and indefinite argument. For purposes of clarification, Applicant emphasizes that primers used for PCR amplification are generally distinct from primers used for sequencing – specifically, PCR requires two primers, one that binds to the sense strand and another that binds to the second strand, while *sequencing* of DNA requires only a *single* primer specific for the one strand of DNA being sequence. Because the references to Digby relate to *sequencing* of DNA, the examiner's assertion that the primers of Digby "inherently" require two primers is simply incorrect. For example, at column 3, lines 1-9 (the citation just prior to the above statement), Digby is referring to "sequencing reactions" and states that "each sequencing reaction contains…a sequencing primer" (note the *singular* definite article) (column 3, line 1-9). Consistent with this, Digby further teaches that if a plurality of genes are to be sequenced, the sequencing mix for each base type independently contains "a plurality of sequencing primers…each one being specific for a *different gene* (or different exon of the same gene)," with each primer having a distinguishable label so that the chain termination fragments for the plurality of genes can be differentiated. Thus, the *sequencing* primers of Digby do not "inherently" bind to both the sense and anti-sense strands of DNA. The sequencing method disclosed by Digby includes only a *single* primer for one region of DNA being sequenced (or *multiple* primers for *different genes*). To repeat, Digby teaches that four reaction vessels are required for each DNA region to be sequenced, which does not meet the required claim limitation of a "single reaction vessel for each DNA region to be sequenced." Nowhere does Digby teach the use of *two* sequencing primers (i.e., one primer for the sense strand and a second primer for the anti-sense strand) for a *single* region of DNA, as required by the claimed invention. The claimed invention requires that each reaction vessel "contain a mixture of region-specific sequence reagents sufficient for sequencing the sense and anti-sense strand of each DNA region to be sequenced." Digby simply does not teach a single reaction vessel that can sequence both the sense and antisense strand.

Because Digby et al. do not teach each and every limitation of the claimed invention, Digby et al. does not anticipate the claimed invention. Accordingly, Applicant respectfully requests that the rejection under 102(e) be withdrawn.

Rejection Under 35 USC § 103(a)

Claims 18-19, 23-24, 30-31, and 35-36 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Digby et al. (U.S. 6,432,634), and Ruano (US. 5,4276,911), in view of Rao (Analytical Biochemistry, vol. 216, pages 1-14 (1994)). Claims 18-19, 23-24, 30-31 and 35-36 each recite specific mole ratios of dideoxynucleotide triphosphate to the corresponding deoxynucleotide triphosphate. Each of the above claims rejected under 103(a) depend from a base claim (not rejected under §103(a)) that requires that the kit contain "as non-region specific reagents four deoxynucleotide triphosphates and at least one dideoxynucleotide triphosphate," which in turn depends directly or indirectly from independent claim 14 (also not rejected under §103(a)).

The claimed invention is described above in connection with the rejection of claims under §102(e).

With respect to Digby et al., the differences between the claimed invention and the teachings of Digby et al. also apply to the rejection under §103(a). Thus, Digby et al. still does not disclose the following claimed elements:

- "a *single* reaction vessel for *each DNA region* to be sequenced";
- a reaction vessel which contains "a mixture of region-specific sequencing reagents sufficient for sequencing the *sense and anti-sense strand* of each DNA region to be sequenced";
- "a primer which specifically binds to the *sense* strand of said DNA region" and is "labeled with a first detectable label" *and* "a primer which specifically binds to the *antisense* strand of said DNA region"; and
- the two primers "flank one of the DNA regions."

Moreover, the examiner repeats the same mischaracterizations of Digby et al. with respect to the rejection §103(a). To the extent that each of claims 18-19, 23-24, 30-31, and 35-36 (that are rejected under §103(a)) depend from one or more of the claims rejected under §102(e), the

differences between those claims (rejected under 102(e) and the Digby et al. reference are also applicable to the rejection of claims under §103(a). Thus, Digby et al. still fails to teach or suggest each and every element of the claims to which rejected claims 18-19, 23-24, 30-31, and 35-36 depend.

The rejection under §103(a) further relies on Rao et al., which the examiner argues discloses a method of direct sequencing of PCR-amplified DNA. The examiner admits that Rao et al. teaches that PCR-amplified genomic DNA is separated "in four different tubes," that Rao et al. does not teach the specific mole ratios recited in claims 18-19, 23-24, 30-31, and 35-36, and that Rao et al. does not teach incorporation of dNTPs into an extending nucleic acid polymerase at a rate which is no less than 0.5 times the ration of incorporation of dNTPs, as required by the claims. The examiner asserts, without support of any evidence or reasoning that "it would have been prima facie obvious to one of ordinary skill in the art at the time of the claimed invention that the mole ratio of ddNTP to dNTP in the kit of Digby would vary depending on the specific polymerase. This statement, however, does not teach or suggest the specific ratios recited in the claimed invention. The statement is clearly based on impermissible hindsight reconstruction and does not therefore satisfy the requirement that the examiner point to a specific teach or suggestion in the prior art. In the absence of a teaching or suggestion of such specific ratios, the examiner's unsupported argument is a mere conclusion coupled with a stereotyped expression that it would have been "prima facie obvious." The argument, however, is without evidentiary support or reasoning, and is therefore without merit.

Moreover, Rao et al. is further distinguishable from the claimed invention on the basis that it discloses a method of generating DNA sequence from PCR-amplified DNA using two locus specific primers that are labeled using the same radiolabel and must, therefore, be in separate containers, otherwise the labeled products could not be distinguished from each other. Thus, the present invention is further distinguishable over the method disclosed by Rao et al., in that the kits of the claimed invention require that the reagents, including multiple detectable labels that can be differentiated, be mixed in the same reaction vessel. Because the method of Rao et al. teach use of a radiolabel in separate containers, Rao et al. does not teach or suggest the present invention, and is in fact incompatible with the claims of the present invention and teach away from the present invention. Thus, Rao et al. does not teach or suggest any of the following limitations required to be present in the claims:

- "a *single* reaction vessel for *each DNA region* to be sequenced";
- a reaction vessel which contains "a mixture of region-specific sequencing reagents sufficient for sequencing the *sense and anti-sense strand* of each DNA region to be sequenced";
- "a primer which specifically binds to the *sense* strand of said DNA region" and is "labeled with a first detectable label" *and* "a primer which specifically binds to the *antisense* strand of said DNA region"; and
- the two primers "flank one of the DNA regions."

For the above reasons, Applicant submits that Rao et al., either alone or in combination with Digby et al. or Ruano et al. (see below), fail to teach or suggest each and every element of the invention, and thus fails to establish a prima facie case of obviousness.

Similarly, Ruano et al. do not teach or suggest the limitations of the present invention, either alone or in combination with Digby et al. and Rao et al. The Examiner states that Ruano et al. teaches that the reagents may be in a single "container," quoting the following passage from Ruano: "The present invention encompasses kits for conducting the aforementioned processes. Such kits include in one or more containers, a set of instructions, and one or more of a thermally stable enzyme." As Applicants have repeatedly emphasized in prior communications with the examiner, the teaching in Ruano of "containers" includes "a set of instructions" which clearly refers to packaging containers (such as a box), not the reaction vessel, since the reaction vessel for the chemical compounds would obviously not contain "a set of instructions." Furthermore, as is evident from Figure 5 in Ruano et al., the labeled primers are placed into separate tubes 12. Ruano et al. thus does not suggest the present invention, because the present invention requires that the reagents be mixed in the same reaction vessel. Thus, Ruano et al. also fails to teach or suggest even one of the following limitations required by the claims:

- "a *single* reaction vessel for *each DNA region* to be sequenced";
- a reaction vessel which contains "a mixture of region-specific sequencing reagents sufficient for sequencing the *sense and anti-sense strand* of each DNA region to be sequenced";

- "a primer which specifically binds to the *sense* strand of said DNA region" and is "labeled with a first detectable label" *and* "a primer which specifically binds to the *antisense* strand of said DNA region"; and
- the two primers "flank one of the DNA regions."

In summary, Digby et al., Rao et al. or Ruano et al., either alone or in combination, fail to teach the above claim limitations. Accordingly, the rejection under §103(a) should be withdrawn.

Intended Use Limitations

The examiner also continues to ignore certain claim limitations, on grounds that the claim limitations constitute an "intended use limitation." The examiner argues that although the prior art references teach primers for copying a single stranded nucleic acid, the claims are broadly written "with intended use limitations" and "do not recite any structural properties or features of the claimed product which distinguishes it over the prior art." The examiner further notes that the MPEP states that

> "a recitation of an intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim."
>
> "language that suggests or makes optional but does not require steps to be performed or does not limit a claim to a particular structure does not limit the scope of a claim or claim limitation."

The Examiner argues that the claim limitations "for each DNA region to be sequenced" and "for sequencing sense and antisense strands" constitute intended use limitations that do not provide structural features.

First, Applicant submits that the patent office rules do not *per se* prohibit intended use limitations – the rules merely require that if such intended use limitations are present they result in structural differences relative to the prior art. In the present case, Applicant has amended claim 14 to affirmatively recite "*a primer* which specifically binds to the sense strand of said DNA region" and "*a primer* which specifically binds to the antisense strand of said DNA region." Applicant submits that the amended claims result in structural differences relative to the prior art – specifically, the primers are required to "specifically bind" to the respective sense strand and anti-sense strand of the DNA region, which clearly impose a *structural limitation that*

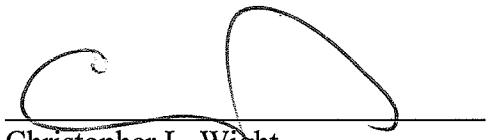
is distinguishable over the prior art. Without primers for both the sense and anti-sense strands, the recited function of "sequencing the sense and anti-sense strand of each DNA region" could not be accomplished. Therefore, the functional language of claim 14 does in fact require the necessary structural limitations to distinguish over the prior art. Applicant therefore submits that the claims can be distinguished over the prior art on the basis of structural limitations in the claims.

The Examiner further argues that because the claims are drawn to a kit (a product) any recitation of a primer must include the *actual sequence* of the primer or the *specific DNA sequence* of the target. This argument is without merit. No such requirement exists, nor has the examiner provided any legal basis for such a requirement. In the present situation, the claimed invention is not directed to *specific* sequences, but rather to a combination of reagents in a kit, which may be used to sequence a variety of different DNA regions. As the examiner should recognize, the particular DNA sequence of the primers will vary, depending on the particular region of DNA being sequenced. Because the claimed invention is not limited to a single specific sequence, the requirement of the examiner to limit the claims to a single sequence is unjustified and unreasonable. Applicant submits that the claim language which recites a "DNA region" and a primer which specifically binds to the sense strand of said DNA region" does not constitute an "intended use limitation" and complies with the statutory requirement of definiteness.

In summary, the claimed invention recites various limitations that are not found in any of the prior art references relied upon by the Examiner. These features are not taught or suggested by the prior art references, either alone or in combination. Applicant has further amended claim 14 to affirmatively recite a primer specific for the sense strand and a primer specific for the anti-sense strand. In view of the fact that the claimed invention does not relate to a particular sequence of primers, and can be applied to any DNA region of interest, the examiner's suggestion that the claims must recite the sequence of the primers or the sequence of the DNA target is without merit. Specific sequence is required only when the invention is itself is directed to a specific to the sequence, which is simply not the case with respect to the claimed invention.

In view of the above claim amendments and arguments presented above, Applicant submits that the rejections have been overcome and respectfully requests that the rejections be withdrawn and the claims allowed.

Respectfully submitted,



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